University of Connecticut
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March 10, 2008

TO: Members of the Committee on Public Health

FROM: Kevin W. Chamberlin, PharmD
Assistant Clinical Professor
UConn School of Pharmacy
&
Board of Directors
Connecticut Chapter of the American Society of Consultant Pharmacists

RE: Testimony on SB 654, AAC the Availability of Prescribed Antiepileptic Drugs

Dear Members of the Committee:

I am an Assistant Clinical Professor of Internal Medicine & Geriatric Pharmacotherapy for the University of Connecticut School of Pharmacy with an active inpatient clinical practice at the University of Connecticut Health Center. As part of my teaching and patient care responsibilities, I educate our pharmacy students, medical students, and medical residents on seizure disorders and the antiepileptic drugs, including a 4-hour lecture to the pharmacy students on this topic. Thus, my written testimony is not only that of my own opinions, but also that backed by medical literature, or lack there of.

Generic substitution of antiepileptic drugs (AEDs) is a controversy beyond the purview of the general public. Many newer AEDs (e.g., zonisamide, lamotrigine, topiramate, gabapentin, oxcarbazepine) have had or soon will have patents expire. All of the older AEDs, except divalproex sodium, are available in generic products.

At the 61st Annual Meeting of the American Epilepsy Society (AES) in Philadelphia, PA on December 1, 2007, Michael Privitera, MD (University of Cincinnati, OH) announced that the AES is in discussions with the US Food and Drug Administration (FDA) to get agreement on a protocol for the development and completion of a valid, controlled, prospective clinical trial to determine "...once and for all whether substitution of brand-name antiepileptic drugs with generic agents may put some patients with epilepsy at undue risk of breakthrough seizures and/or toxicity."[1]

Current FDA bioequivalency regulations require the area-under-the-curve and absorption rate of a generic product to be within 80 – 125% of mean values for the brand product and for the 90% confidence interval around the geometric mean for the generic product to be within the 80 – 125% range for the brand product. The FDA currently makes no distinction in these standards for drugs or disease states that are complex of critical.

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Generic drug manufacturing rests on "bioequivalence." A generic drug must be determined to be "bioequivalent" to its name brand predecessor drug before the FDA will call it a generic. In order for a drug to be bioequivalent the drug must have the same active ingredients, dosage form, strength, and route of administration as the original. The two pharmacokinetic measurements, area under the drug concentration-time curve (AUC) and maximum concentration (C_{max}), are used to determine bioequivalence. If a drug is determined to be bioequivalent, it is also thought to be therapeutically equivalent. While generics should also have no greater potential for adverse effects, generics are allowed to have differences in color, flavor, shape, appearance, and shelf-life. They are also allowed to have different salts or esters of the active drug. Some studies have shown that different salts of the same active drug can have distinct chemical properties.[2 3 4 5]

Many of these resolutions and petitions to change the standards for AEDs include provisions (such as SB 654) that prohibit a pharmacist from making generic substitutions for AEDs.[6] These proposals come from pharmaceutical manufacturers, legislative groups, patient advocacy groups, and professional organizations.

A number of pieces of "less than idea" pieces of literature on this topic are available for review. One example, a publication by Andrew Wilner, MD, is often quoted in the literature in favor of legislation similar to SB 654, and yet a number of flaws can be identified that even the author suggests are limitations to his findings: (a) the study is retrospective [a weakness]; (b) there was a 4.7% response rate to his survey [a weakness that is not substantiated by a power calculation to determine the number needed to respond to have a valid study]; (c) the survey was not stated as being anonymous, possibly deterring responders from participating [a weakness]; (d) the survey results were not substantiated by documentation from chart reviews – they were simply from 'memory' [a weakness].[7]

From: Perucca E, et al.[8]

> **Quality of the evidence and interpretation of available data**
> No randomized controlled trials (RCTs) were identified that compared the effects of generic AEDs and corresponding brand products in a sizeable number of patients with epilepsy. The only identified RCT that enrolled at least 50 subjects was a comparative crossover study of 64 patients assigned to receive in random sequence a generic and a brand product of valproic acid, each for four-week periods. This study, of limited quality for its modest sample size and its short duration, did not detect any difference in seizure control and plasma drug levels between the two treatment periods (Vadney and Kraushaar, 1997).
>
> In contrast to the lack of controlled studies, there are several published reports of loss or worsening of seizure control (Koch and Allen, 1978; Pedersen and Dam, 1985; McDonald, 1987; Wyllie et al., 1987; Sachdeo and Belendiuk, 1987; Hartley et al., 1990;Welty et al., 1992; Jain, 1993; Meyer and Straughn, 1993; Guberman and Corman, 2000; Burkhardt et al., 2004; Wilner, 2004; Haskins et al., 2005) or appearance of adverse events (Finestone and Williams, 1985; Gilman et al, 1993; Brown et al., 1998; Guberman and Corman, 2000; Wilner, 2004; Haskins et al., 2005) following

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substitution of a brand AED with a generic. Many of these reports date back several years, when regulatory requirements for the approval of generics were not as stringent as those currently in force in major industrialized countries (Richens, 1997; American Medical Association, 2006) and therefore some products of inadequate quality found their way into the market (Bochner et al., 1972; Sansom et al., 1975; Manson et al., 1975; Stewart et al., 1975; Tammisto et al., 1976; Hodges et al.,1986; Mikati et al., 1992; Soryal and Richens, 1992; Meyer et al., 1992; Rosenbaum et al., 1994). In 1988, the U.S. Food and Drug Administration (FDA) set up a special committee to investigate these issues. Between 1988 and 2000, the FDA investigated more than 60 reports of potential inequivalence of generic products, and has been unable to document a single example of therapeutic failure when an FDA-designated therapeutically equivalent generic product, which was manufactured to meet its approved specifications, was substituted for the corresponding brand-name drug listed in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations (Henney, 2000).

The frequency with which, disregarding any attribution of cause-effect relationship, the switch from a brand product to a generic (or vice versa) is associated with a change in clinical status cannot be established from anecdotal reports: surveys using questionnaires compiled by patients with epilepsy variably reported frequencies in the order of 11% (Crawford et al., 1996), 14% (Guberman and Coman, 2000), 23% (Haskins et al., 2005), or even 46% (Chappell, 1993), but these estimates are probably influenced by selection bias (the patients who believe to have been affected adversely by the switch are also those who are most likely to return the questionnaire) and by the subjective, retrospective and uncontrolled methodology applied in these surveys. Moreover, reported "problems" do not always refer to a worsening in seizure control: for example, in the survey conducted by Crawford et al. (1996), 11% of patients reported a "validated problem," but only one patient (0.4%) complained of reemergence of seizures after 12 months of complete control and only eight patients (3%) reported "increased seizure frequency." A report on an initiative by the International Bureau for Epilepsy, a patients' organization which expressed concerns about the "risks" associated with generic substitution, estimated that the switch from one product to another may involve a risk of breakthrough seizures in 1 to 2% of cases (Van Emmerink, 2005).

While there is no doubt that in some cases a switch between products can be associated with an alteration in clinical status, a critical assessment of available evidence does not allow us to establish a cause–effect relation, at least for the majority of reported cases. In a disorder such as epilepsy, which is known to be associated with spontaneous fluctuation in the manifestations of the disease, a transient deterioration in seizure control after changing a pharmaceutical product may be due simply to chance or to factors which are unrelated to the product prescribed (for example, a change in compliance). This is well illustrated by the controlled study performed by Vadney and Kraushaar (1997): of 64 patients randomized to generic substitution in this study, 17 had been free from seizures during the 12 months preceding randomization. Two of these patients suffered a seizure recurrence during the study, but in both cases the reemergence of seizures occurred during the period in which the product takenwas the same utilized by the same subjects during the 12 months prior to the study!

Some pharmacoeconomic evaluations have been published which suggest that the possible costs of managing the potential disease deterioration or adverse effects resulting from generic

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substitution may outweigh the savings from the lower price of generics (Jumao-as et al., 1989; Crawford et al., 1996; Argumosa and Herranz, 2005). The working group considered these estimates unreliable, because no unbiased quantitative evidence is available on the possible adverse consequences of generic substitution. By contrast, it is a fact that the difference in price between a brand product and a generic can be substantial, sometimes as much as 10-fold (Vadney and Kraushaar, 1997), even though at times the introduction of a generic may also lead to a reduction in the price of the brand product.

Overall, generic AEDs meeting current regulatory criteria for bioequivalence represent a valuable choice in the management of epilepsy by allowing a substantial reduction in treatment costs, particularly in patients initiating monotherapy or adjunctive treatment, and in those with persistent seizures.[8] Careful review of the literature reveals no adequately powered randomized controlled trials that assessed the risk / benefit ratio of generic substitution.

I encourage members of the committee to review the attached documents from Welty and the subsequent editorial comment on it by Dr. Randy Hatton.

Question to the Committee: *Should not the passing of such a bill wait until the FDA and AES have conducted the study discussed in reference 1 (3rd paragraph of this letter)?*

Respectfully submitted,

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/es/
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EDITORIAL

Pharmacy and Generic Substitution of Antiepileptic Drugs: Missing in Action?

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Generic substitution of antiepileptic drugs is an issue that is gathering a lot of attention in the neurology community but is not receiving much attention within pharmacy. Several proposals have been drafted that restrict a pharmacist's decision-making in generic substitution. These proposals highlight concerns about the pharmacy community related to generic substitution. Careful consideration needs to be given to these issues by pharmacists and pharmacy professional organizations. Unless pharmacy as a profession takes strong positions in support of a pharmacist's ability to make decisions about pharmacotherapy and addresses many of the pharmacy-related problems of generic substitution, policies that negatively impact pharmacy will be established.

KEY WORDS: antiepileptic drugs, epilepsy, generic substitution, pharmacy practice.

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Public policy decisions are often made without full understanding of the circumstances and issues surrounding the decision or with a lack of data needed for rational policy-making. Generic substitution of antiepileptic drugs (AEDs) is a controversy brewing outside the purview of the general public or broad circles of the pharmacy profession. Many newer AEDs (eg, zonisamide, lamotrigine, topiramate, gabapentin, oxcarbazepine) have had or soon will have patents expire. All of the older AEDs, except divalproex sodium, are available in generic products.

Within the neurology community, there is concern about generic substitution of AEDs. This is due to narrow therapeutic windows for some drugs, complex pharmaceutics and pharmacokinetics of older agents, and severe consequences if a generic drug fails. A seizure that could result in harm to the patient or others has major lifestyle implications.

Current Food and Drug Administration (FDA) bioequivalency regulations require the area-under-the-curve and absorption rate of a generic product to be within 80–125% of mean values for the brand product and for the 90% confidence interval around the geometric mean for the generic product to be within the 80–125% range for the brand product. The FDA makes no distinction in these standards for drugs or disease states that are complex or critical. As a result, many have argued that standards for AEDs need to be stricter due to the complexities of these drugs and epilepsy. Such revisions may be reasonable and require thoughtful consideration. However, many of these resolutions and petitions include provisions to prohibit a pharmacist from making generic substitutions for AEDs.[1-5] These proposals come from pharmaceutical manufacturers, legislative groups, patient advocacy groups, and professional organizations. A major effort is underway to have state legislatures pass these proposals into law. While details of these proposals are important to understand, the purpose of this editorial is to focus on the professional issues that these proposed policies raise.

The main idea being put forward is that pharmacists not be permitted to make generic substitutions without specific, written permission of the prescribing physician for every AED substitution. In some cases, the recommendations require the pharmacist to also have approval of the patient. Many pharmacists will complain about the time, effort, and money required in obtaining physician or patient approval. However, the issue cuts at something far deeper and more fundamental to pharmacy as a profession. Pharmacists are and must be viewed as independent healthcare providers in the community. They possess the expertise to understand the issues surrounding generic substitution and, with the advent of the entry-level Doctor of Pharmacy curriculum, have the clinical acumen to make sound decisions regarding generic substitution and pharmacotherapy.

Author information provided at the end of the text.

This idea is basic to collaborative practice agreements and prescriptive authority legislation that has been implemented in the majority of the states. In most of this legislation, the pharmacist is given general approval by the physician to prescribe medication in preapproved situations without seeking approval for individual patients. Current proposals to limited generic substitution of AEDs would prevent pharmacists from practicing in this manner. Additionally, the concept of pharmacists being providers of health care forms the basis of the Medication Therapy Management legislation in the Medicare Part D plan. A proposal to prevent pharmacists from making generic substitutions without approval of a physician negates these basic principles. It also ignores volumes of data supportive of programs permitting pharmacist management of drug therapy. If these restrictive proposals are enacted, the profession of pharmacy will suffer a setback of several decades in its drive to have pharmacists be providers of health care rather than mere dispensers of medication.

While these proposals are disconcerting and seem to harm the progress that pharmacy has made as a profession, a question must be asked as to why they are being considered. Obviously, reasons outside of pharmacy exist that cause people to consider restrictions on the autonomy and professional activities of pharmacists in relationship to patient care. These points can be argued and discussed in detail in other places. However, pharmacy as a profession must consider the possibility that we have contributed to, and in some cases, encouraged policy makers to restrict our professional duties and activities.

The following are examples of practices that may have led to resolutions like those proposed for generic substitution of AEDs. Too often, pharmacists have succumbed to insurance companies, managed care organizations, governmental programs, and pharmacy benefit managers who require automatic substitution of generic products. Typically, third-party payers make formulary decisions predominantly on a financial basis; the well-being of the individual patient is not the primary consideration. In the case of AED generic substitution, there are clinical situations where generic substitution is not in the best interest of the patient. For example, patients who are seizure-free with their current pharmacotherapy regimen may have a seizure when switched to a generic product.[6,7] If this happens, those patients could injure themselves or others and will lose their ability to drive a vehicle, thus having a negative impact on their job and lifestyle and placing increased burden on their family or caregivers. Additionally, such proposals add to the general perception that generic substitution is ill-advised and potentially harmful. However, policies and some state legislation dictate generic substitution regardless of the clinical situation and possible consequences for the patient. Rather than challenging these policies and laws or proposing alternative approaches that give greater weight to each patient, we simply accept the policies and laws. If pharmacists are to act as independent healthcare providers, we need to fight for their right to make independent clinical decisions about generic substitution without being forced by third-party payers or government to substitute generic products, especially in the case of epilepsy and AEDs.

It can be argued that the pharmacist is not really forced in any situation to dispense a generic product. However, in nearly a third of the states, state law mandates the dispensing of generic products if the physician has not signed for a brand name product. Outside of these laws, policies do allow patients to decide whether they receive a brand or generic product. Accompanying these policies for third-party payers, there is typically a requirement that the patient pays larger copayments or covers the entire cost of the prescription. A large number of individuals with epilepsy are unemployed or underemployed due to their disorder. As a result, many of these people have little or no insurance coverage for prescriptions. Even an increase in copayments for prescriptions can place a large financial burden on patients with epilepsy, in essence forcing them to use a generic product even when it may not be in their best interest. Policies that restrict the pharmacist and patient in determining whether a generic or brand name AED is the best choice for their disorder in essence restrict access to care and do not take into account the specific needs of the patient. As healthcare providers, pharmacists need to be strong advocates for patients by arguing for openness and no restrictions in the patient's ability to receive optimal care.

Pharmacists are also encouraged to substitute generic products through financial incentives. A combination of low maximum allowable costs for drugs with generic equivalents and current dispensing fees can place pharmacists in a difficult financial situation. If pharmacists do not substitute the least expensive product, they may lose money. Rather than carefully evaluating the individual needs and clinical situation of each patient, pharmacists often substitute a generic product because it is financially expedient. Financial and business concerns take precedence over what is medically best for the individual patient. When this occurs, our clinical training is muted and we become business people rather than providers of health care.

Whether it is due to third-party payer mandates or financial incentives, we pharmacists typically make the substitution, tell the patient that the product is the same drug as prescribed, but in a generic form, and inform no one other than the third-party payer that the substitution has been made. We pride ourselves on our independence to make this type of decision but forget that we are part of a healthcare team. Repeatedly, the Institute of Medicine has identified the lack of teamwork as a major impediment to improving the quality of health care in the US.[8-10] To enhance teamwork, pharmacists must voluntarily take the initiative in weighing the decision regarding generic substitution as

it relates to each patient case and informing other members of the healthcare team when generic medications are substituted. Some pharmacists and practice settings (eg, some mail-order pharmacies) do attempt to make this a standard of practice. But in the absence of a profession-wide commitment to collaboration, those outside of pharmacy will dictate policies and regulations that are very restrictive and impair our ability to exercise professional responsibilities and judgments. We must proactively work at improving communications with physicians regarding the issues surrounding generic substitution of AEDs and routinely informing physicians of decisions regarding individual patients.

For a disorder like epilepsy, it is not always wise for routine generic substitution to be enforced. Certainly, pharmacists have the knowledge and skills to make these types of clinical decisions, but often do not or are forced to not take these opportunities. Pharmacy as a profession needs to aggressively propose alternatives to blanket generic substitution plans, allowing individual pharmacists to make independent clinical decisions without suffering financial penalties. It can be argued that there are no real alternatives. However, in a recent interview, Mark McClellan MD, the former head of the FDA and the Centers for Medicare and Medicaid Services, notes that in consumer-directed health care, generic substitution is not always the answer.[11] He states that Pitney Bowes' consumer-directed health plan allows for patients with some conditions, like diabetes or heart disease, to receive brand or generic products and does not require generic substitution. According to McClellan, the result is improved adherence to medications and overall reductions in healthcare costs. Certainly, epilepsy could be classified with diabetes and heart disease as a disorder that does not fit the typical standards. Innovative approaches to generic substitution like this are needed to refocus the system on patient care for patients with epilepsy.

Within the system of generic substitution, pharmacists allow practices that may jeopardize patient care, especially in a disorder like epilepsy, and add to public mistrust and confusion. Practices such as using whatever AB-rated product is cheapest for the month or utilizing manufacturers or repackagers who routinely change sources for their generic products promote inconsistency in the response of patients to their medication and promote the idea that generic drugs are not reliable. Additionally, when a patient transfers a prescription to another pharmacy, there is a good chance that a different generic product will be dispensed. As pharmacists, we have the responsibility to ensure that the patient receives the same generic product with every refill by consistently stocking the same generic products and avoiding manufacturers who are notorious for switching sources of their products. Through purchasing agreements, we can hold wholesalers accountable for a supply chain that consistently provides the same generic products.

In negotiating contracts with third-party payers, we need to propose innovative approaches that provide incentives for improved pharmacotherapeutic outcomes in patients rather than controlling practice through financial or other disincentives. Pharmacists can also determine what generic product the patient has been receiving and use the same product when a patient transfers a prescription from one pharmacy to another. Additionally, we must voluntarily and aggressively participate as members of the healthcare team, informing physicians, nurses, and physician assistants of actions related to generic substitution or other pharmacotherapy issues related to each patient. As healthcare professionals who are responsible to the public and our patients for pharmacotherapy and its outcome, we must attempt to do everything possible to guarantee that any generic substitution is done in a manner that provides maximal benefit to individual patients.

Beyond what individual pharmacists can do, professional organizations like the American Pharmacists Association, the American Society of Health-System Pharmacists, the American College of Clinical Pharmacy, and the National Community Pharmacists Association must develop, endorse, and lobby for policies that recognize the rightful place of pharmacists in making decisions about generic substitution. These positions need to go beyond simply supporting generic substitution; they must recognize the ability of pharmacists to make appropriate clinical decisions concerning generic substitution for individual patients, without restrictions or coercion. Professional organizations need to work closely with their membership to understand all of the issues surrounding generic substitution and develop methods to avoid and overcome the pitfalls associated with common pharmacy practices in this area. Additionally, professional organizations are in a position to collectively address the issues of generic substitution of AEDs with third-party payers, government agencies, and legislative bodies, supporting alternatives that benefit patients, pharmacists, and payers of health care. Without this type of leadership, we may be saddled with policies that are encumbering for patients and pharmacists.

Even with AEDs, generic substitution can be an effective method of reducing costs of medications and improving access to care. However, unless pharmacists aggressively address the problems inherent in generic substitution and assert their position as independent healthcare providers in collaboration with physicians, individuals and groups outside of the pharmacy profession will restrict our ability to be independent practitioners and force us to accept policies that are harmful first to our patients and ultimately to our profession.

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EXTRACTO

La substitución de genéricos de medicamentos antiepilépticos es un asunto que ha generado mucha atención en la comunidad de neurología, pero que no ha recibido mucha atención dentro de la comunidad farmacéutica. Algunas de las propuestas que han sido redactadas restringen la decisión del farmacéutico de tomar decisiones en cuanto a la substitución de genéricos. Estas propuestas enfatizan la preocupación sobre la comunidad farmacéutica relacionado a la substitución de geneicos. Los farmacéuticos y las organizaciones del profesional de farmacia deben proveerle una consideración cuidadosa a este asunto. Hasta que la profesión de farmacia tome una posición enfatica que apoye la capacidad del farmacéutico para tomar decisiones en cuanto a la farmacoterapia y se exprese en relación a los problemas relacionados a la substitución de medicamentos, se establecerán políticas que afecten de forma negativa la profesión de farmacia.

Annette Perez

RÉSUMÉ

La substitution générique des anticonvulsivants est une question attirant beaucoup l'attention de la communauté des sciences neurologiques mais recevant peu d'attention de la communauté pharmaceutique. Des projets de propositions pour restreindre les activités de substitution de médicaments génériques par le pharmacien ont été rédigés. Ces propositions mettent en lumière les craintes face à la substitution générique par les pharmaciens. Les pharmaciens et les associations professionnelles pharmaceutiques devraient évaluer ces points avec beaucoup d'attention. La communauté pharmaceutique devrait se positionner sur les différents enjeux et problèmes reliés à la substitution des médicaments. Des politiques restrictives affectant négativement la pratique de la pharmacie risquent d'être établies à moins d'une prise de position ferme par la communauté pharmaceutique supportant les capacités du pharmacien à poser un jugement clinique sur la pharmacothérapie. Le rôle du pharmacien comme prestataire de soins autonome travaillant en collaboration avec les médecins doit être défendu avec vigueur par les pharmaciens et leurs associations professionnelles.

Marie-Claude Vanier

of the disease.[1] In the letter to the editor, the author postulates that the same mechanism is the reason that naltrexone has been found to help autistic patients.[4] Naltrexone is an opiate antagonist approved by the Food and Drug Administration (FDA) for the treatment of alcohol dependence and for the reversal of effects of an opioid.

There are no published scientific studies or case reports that have documented the use of naltrexone for MS. However, much anecdotal information can be found on the Internet: a search for naltrexone and multiple sclerosis yielded over 60 000 results. Numerous Web sites are dedicated to spreading the word on this potential therapy. Several Web sites of compounding pharmacies advertise their experience in compounding formulations of low-dose naltrexone. However, as healthcare professionals know, Internet-based anecdotal evidence is not a replacement for sound scientific data.

In the past, the National Multiple Sclerosis Society (NMSS) has recommended that patients with MS avoid naltrexone.[5] Many Web sites state that naltrexone works in MS by boosting the immune system.[6] Because MS is thought to be an autoimmune disease, anything that may boost the immune system has the potential of worsening the disease. Current FDA-approved treatments, including interferon-β and glatiramer, mitoxantrone, and natalizumab, modulate the immune response rather than boost it.[1] However, the NMSS is now encouraging clinical trials on the subject.[7]

Clinical trials involving the use of naltrexone in MS patients are currently underway.[7,8] The results of these studies, especially those involving patients with MS,[8] will be important.

Due to the limitations of the conventional therapies for MS, including the potential for serious adverse events, inconvenient administration, and high costs, many patients with MS are eager to try low-dose naltrexone. Given the large worldwide interest in this subject, data from clinical trials will be of great interest.

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Comment: Pharmacy and Generic Substitution of Antiepileptic Drugs: Missing in Action?

TO THE EDITOR: I have concerns about Dr. Welty's recent editorial regarding the generic interchange of antiepileptic drugs (AEDs).[1] A premise of this editorial is that the bioequivalency standards of the Food and Drug Administration (FDA) are inadequate for specific drugs or diseases. There is insufficient evidence to draw this conclusion.

The FDA's bioequivalency standards are rigorous and are designed to allow for generic interchange with the same consistency as lot-to-lot variability of brand-name drugs.[2] If there are problems with the FDA's standards, then they should be changed. The first step, however, is to prove scientifically that there are problems with specific drugs, patient populations (eg, pediatrics), or diseases. At this point, there is only anecdotal evidence. There are no published randomized controlled trials that have demonstrated that A-rated AEDs are not bioequivalent to branded AEDs. In fact, FDA-sponsored studies for generic carbamazepine showed no difference in safety or efficacy for brand-names of carbamazepine.[2]

Case reports are limited by lack of control groups. When patients are switched to a generic drug and a problem occurs, patients and prescribers associate the problem with the generic drug. However, problems occur every day when patients remain on a brand-name AED. In this case, the problem is not blamed on the brand. Randomized, blinded controlled trials are needed to avoid this bias.

When Coumadin came off patent and generic versions of warfarin first became available, there were concerns that the generic versions would result in unnecessary variation in international normalized ratios (INRs) and, possibly, worse patient outcomes.[3,4] Randomized trials do not support anecdotal observations of problems with INRs,[5] and a recent large epidemiologic study of generic and brand-name warfarin did not find any differences in INR monitoring or patient outcomes.[6]

If controlled data generated for AEDs reveal problems, the FDA should make its standards more rigorous or exempt certain drugs from its equivalency standards. Further, various lots of brand-name drugs should be studied to ensure that they are bioequivalent. Any brand manufacturing change should require evidence that the brand continues to meet more stringent standards.

I agree with Dr. Welty that state-by-state changes in laws that forbid generic interchange of drugs based on diseases are not a positive development. If these laws are passed, a pharmacist could not easily dispense generic gabapentin to a patient prescribed Neurontin for pain unless the prescriber were required to put the indication for use (ie, epilepsy) on the prescription. In Florida, where I reside, this practice would not differ much from current law, which forbids generic interchange when "medically necessary" is written on the face of an AED prescription.

The forced dispensing of brand-name drugs will increase patients' out-of-pocket expenses and/or prescribers' and pharmacists' workloads. At best, if patients cannot afford higher copayments for brand-name drugs, written authorization for generic prescriptions will generate telephone calls and faxes. At worst, if patients are unable to pay for higher priced brand-name drugs, patient adherence could be affected.

Payors, whether patients or third parties, should not be expected to increase their expenditures by paying for brand-name drugs without evidence to support the higher costs. The group that will definitely benefit financially from mandated brand-name dispensing will be brand-name manufacturers, who will have exclusivity that will never expire. It is interesting to note that state legislative initiatives to limit generic interchanges are occurring at a time when more widely prescribed drugs are coming off patent and drug companies' revenues are falling. It frightens

Comments on articles previously published are submitted to the authors of those articles. When no reply is published, either the author chose not to respond or did not do so in a timely fashion. Comments and replies are not peer reviewed.–ED.

me when "policy makers" (ie, politicians) make unscientific healthcare decisions.

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AUTHOR'S REPLY: I greatly appreciate the comments from Dr. Hatton and the issues raised by him with regard to my editorial. This type of open discussion and dialogue is needed to determine the appropriate course of action for policy and legislative decisions. In reality, our views are probably not extremely disparate. However, several points that Dr. Hatton presents need to be understood completely within the context of the unique features of epilepsy.

Dr. Hatton correctly notes that the FDA standards for bioequivalency are rigorous and scientifically sound. Generally, those standards are sufficient for most disease states and their management. Indeed, a self-study on the quality of FDA decisions regarding bioequivalency for all approved generic drugs showed that means for bioequivalence parameters were within 5% of the innovator product.[1] Even in light of these facts, there remains a risk, albeit small, that an approved generic AED is not equivalent to the innovator product. Because the failure of generic AEDs has the potential to bring acute and chronic harm to the patient (eg, injury during a seizure, loss of employment, death) and harm to others (eg, injury in an automobile accident due to a seizure), it is legitimate to ask whether even the small risk of nonequivalence that accompanies current FDA standards is at an acceptable level for a disease such as epilepsy. In other words, would patients with epilepsy, as well as the public, be better served by stricter bioequivalence standards to reduce the risk of failure with a generic product? This question deserves careful consideration and study.

There is a paucity of data (especially from controlled clinical trials) to indicate a problem with generic substitution of AEDs. However, some studies indicate potential problems, at least with certain drugs or formulations. Burkhardt et al.[2] reported reduced serum concentrations of phenytoin and increased seizures in 8 patients who were switched to generically equivalent phenytoin. In a study of approved generically equivalent sustained-release carbamazepine preparations, Mayer et al.[3] demonstrated significant differences in serum concentrations achieved with the 2 products used in the same individuals. Although these products were approved in Germany, they did meet the FDA and European Union standards for bioequivalence. A review of a pharmacy claims database in Canada showed that 12.9% of patients who were switched to generic lamotrigine switched back to the brand-name product.[4] In the same study, approximately 20% of patients who were switched to generic clobazam or divalproex returned to the brand-name products. Additionally, use of added AEDs significantly increased in patients who switched to and remained on generic products. While none of these studies provides definitive proof of a problem with generic AEDs, they raise the possibility that current FDA standards are not sufficient for determining bioequivalence of AEDs.

Dr. Hatton compares concerns about AEDs with the controversy that has surrounded the use of generic warfarin. Some of the issues with AEDs may be similar to those raised about warfarin; however, there is a major difference between generic substitution of warfarin and generic substitution of AEDs. With warfarin, the international normalized ratio is an easily measured and validated laboratory test that accurately predicts the risk of bleeding or thrombosis. The effects of warfarin are routinely monitored using this test, and dosages are adjusted to maintain the INR within well-established therapeutic ranges. Careful monitoring of the INR reduces the probability of clinical problems associated with generic substitution of warfarin. Unfortunately, in epilepsy there is no test or assessment method that predicts the risk of a seizure, other than a patient consistently receiving appropriate doses of AEDs. Even the measurement of AED serum concentrations has not correlated with effective control of seizures.[5] The only true indicator of a generic drug failure in epilepsy is a breakthrough seizure. When the treatment goal is elimination of seizures, it is inappropriate to place the patient at risk of a seizure and the harm it can cause to serve as an indicator of a generic AED failure. Because there is no test that predicts the risk of a seizure, the comparison with generic warfarin is neither equivalent nor appropriate.

Finally, I agree with Dr. Hatton that it is frightening to have uninformed individuals making policy and legislative decisions about health care. Reactionary positions are often fueled by misinformation or inadequate understanding. People at all levels of the decision-making process about the regulation of AEDs should possess a thorough understanding of epilepsy and its management in addition to having data about bioequivalence and drug formulations. It would seem most prudent to convene a national dialogue and study of this topic to determine the best policies and approaches regarding the issues surrounding generic substitution of AEDs. Perhaps my editorial and the comments by Dr. Hatton will spur additional dialogue and lead to a national meeting to consider these issues.

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Correction: Rates of Adverse Events of Long-Acting Opioids in a State Medicaid Program

In this article (2007;41:921-8), in the second paragraph under "Results," the second sentence should read "For the primary outcome of time to first ED or hospitalization for opioid-related adverse events, subjects in the oxycodone ER cohort were 55% less likely to have an event compared with the morphine ER cohort." The "Results" section of the abstract should be similarly corrected from 35% to 55%.

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Letters are subject to review prior to acceptance. They should address areas related to pharmacy practice, research, or education, or articles recently published. Corrections of previously published material also are accepted. Letters are limited to no more than five authors. In cases where adverse drug effects are described, the Naranjo ADR probability scale should be used to determine the likelihood that the adverse effect was drug-related (Clin Pharmacol Ther 1981;30:239-45). Text: limit 500 words. References: limit 5. Art: limit 1 table or figure.